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Mesalazine controlled release oral pharmaceutical compositions
Mesalazine enthaltende pharmazeutische Zusammensetzungen mit gesteueter Freisetzung
Compositions pharmaceutiques orales à libération régulée à base de mésalazine

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The present invention relates to controlled release oral pharmaceutical compositions containing as active ingredient 5-amino salicylic acid, also named mesalazine.

BACKGROUND OF THE INVENTION

Mesalazine is used in the treatment of Chron’s disease and ulcerative colitis thanks to its antiinflammatory activity on the intestinal mucus. Controlled-release formulations of mesalazine are disclosed in WO 95/16451, EP 0 453 001, EP 0 377 477.

The preparation of a sustained, controlled, delayed or anyhow modified release form can be carried out according to different known techniques:

1. The use of inert matrices, in which the main component of the matrix structure opposes some resistance to the penetration of the solvent due to the poor affinity towards aqueous fluids; such property being known as lipophilia.
2. The use of hydrophilic matrices, in which the main component of the matrix structure opposes high resistance to the progress of the solvent, in that the presence of strongly hydrophilic groups in its chains, mainly branched, remarkably increases viscosity inside the hydrated layer.
3. The use of bioerodible matrices, which are capable of being degraded by the enzymes of some biological compartment.

All the procedures listed above suffer, however, from drawbacks and imperfections.

Inert matrices, for example, generally entail nonlinear, but exponential, release of the active ingredient.

Hydrophilic matrices have a linear behaviour until a certain fraction of active ingredient has been released, then they significantly deviate from linear release.

Bioerodible matrices are ideal to carry out the so-called "site-release", but they involve the problem of finding the suitable enzyme or reactive to degradation. Furthermore, they frequently release in situ metabolites that are not wholly toxicologically inert.

A number of formulations based on inert lipophilic matrices have been described: Drug Dev. Ind. Pharm. 13 (6), 1001-1022, (1987) discloses a process making use of varying amounts of colloidal silica as a porization element for a lipophilic inert matrix in which the active ingredient is incorporated.

The same notion of canalization of an inert matrix is described in US 4,608,248 in which a small amount of a hydrophilic polymer is mixed with the substances forming an inert matrix, in a non sequential compenetrating of different matrix materials.

EP 375,063 discloses a technique for the preparation of multiparticulate granules for the controlled-release of the active ingredient which comprises co-dissolution of polymers or suitable substances to form a inert matrix with the active ingredient and the subsequent deposition of said solution on an inert carrier which acts as the core of the device. Alternatively, the inert carrier is kneaded with the solution containing the inert polymer and the active ingredient, then the organic solvent used for their dissolution is evaporated off to obtain a solid residue. The resulting structure is a "reservoir", i.e. is not macroscopically homogeneous along all the symmetry axis of the final form.

The same "reservoir" structure is also described in Chem. Pharm. Bull. 46 (3), 531-533, (1998) which improves the application through an annealing technique of the inert polymer layer which is deposited on the surface of the pellets.

To the "reservoir" structure also belong the products obtained according to the technique described in WO 93/00889 which discloses a process for the preparation of pellets in hydrophilic matrix which comprises:

- dissolution of the active ingredient with gastro-resistant hydrophilic polymers in organic solvents;
- drying of said suspension;
- subsequent kneading and formulation of the pellets in a hydrophilic or lipophilic matrix without distinction of effectiveness between the two types of application.

EP 0 453 001 discloses a multiparticulate with "reservoir" structure inserted in a hydrophilic matrix. The basic multiparticulate utilizes two coating membranes to decrease the release rate of the active ingredient, a pH-dependent membrane with the purpose of gastric protection and a pH-independent methacrylic membrane with the purpose of slowing down the penetration of the aqueous fluid.

WO 95/16451 discloses a composition only formed by a hydrophilic matrix coated with a gastro-resistant film for controlling the dissolution rate of mesalazine.

When preparing sustained-, controlled- release dosage forms of a medicament topically active in the gastrointestinal tract, it is important to ensure a controlled release from the first phases following administration, i.e. when the inert matrices have the maximum release rate inside the logarithmic phase, namely the higher deviation from linear release.

Said object has been attained by the present invention, which also allows to prepare compositions characterized by a high content in active ingredient.

DISCLOSURE OF THE INVENTION

The invention provides controlled release oral pharmaceutical compositions containing 5-amino-salicylic acid as the active ingredient, comprising:
a) an inner lipophilic matrix consisting of substances with melting point below 90°C in which the active ingredient is at least partially inglobated;
b) an outer hydrophilic matrix in which the lipophilic matrix is dispersed;

wherein the composition releases up to 90% of the active agent within 8 hours of immersion in simulated enteric juice.

**DETAILED DISCLOSURE OF THE INVENTION**

[0018] The compositions of the invention can be obtained with a method comprising the following steps:

a) the active ingredient is first inglobated in a low melting excipient or mixture of excipients, while heating to soften and/or melt the excipient itself, which thereby incorporates the active ingredient by simple dispersion.

After cooling at room temperature an inert matrix forms, which can be reduced in size to obtain matrix granules containing the active ingredient particles.

b) the inert matrix granules are subsequently mixed together with one or more hydrophilic water-swelling excipients.

[0019] This way, when the tablet is contacted with biological fluids, a high viscosity swollen layer is formed, which coordinates the solvent molecules and acts as a barrier to penetration of the aqueous fluid itself inside the new structure. Said barrier antagonizes the starting "burst effect" caused by the dissolution of the medication inglobated inside the inert matrix, which is in its turn inside the hydrophilic matrix.

[0020] The lipophilic matrix consists of substances selected from unsaturated and/or hydrogenated fatty acids, salts, esters or amides thereof, fatty acids mono-, di- or triglycerids, waxes, ceramides, cholesterol derivatives or mixtures thereof having melting point within the range of 40 to 90°C.

[0021] If desired, a fatty acid calcium salt may be incorporated in the lipophilic matrix which is subsequently dispersed in a hydrophilic matrix prepared with alginic acid, thus remarkably increasing the hydrophilic matrix viscosity following penetration of the solvent front until contact with the lipophilic matrix granules dispersed inside.

[0022] The weight content of the active ingredient in the lipophilic matrix usually ranges from 5 to 95%.

[0023] The inert lipophilic matrix is reduced into granules by an extrusion and/or granulation process, or any other known processes which retain the homogeneous dispersion and matrix structure of the starting mixture.

[0024] The hydrophilic matrix consists of excipients known as hydrogels, i.e. substances which pass from the dry state to the hydrated one, undergo the so-called "molecular relaxation", namely a remarkable increase in mass and weight following the coordination of a large number of water molecules by the polar groups present in the polymeric chains of the excipients themselves.

[0025] Examples of hydrogels which can be used according to the invention are compounds selected from polymers or copolymers of acrylic or methacrylic acid, alkylvinyl polymers, hydroxyalkyl celluloses, carboxyalkyl celluloses, polysaccharides, dextrins, pectins, starches and derivatives, natural or synthetic gums, alginic acid.

[0026] The lipophilic matrix granules containing the active ingredient are mixed with hydrophilic compounds cited above in a weight ratio typically ranging from 100:0.5 to 100:20 (lipophilic matrix: hydrophilic matrix). Part of mesalazine can optionally be mixed with hydrophilic substances to provide compositions in which the active ingredient is dispersed both in the lipophilic and the hydrophilic matrix, said compositions being preferably in the form of tablets, capsules and/or minitablets.

[0027] The compression of the mixture of lipophilic matrix, hydrogel-forming compounds and, optionally, active ingredient not inglobated in the lipophilic matrix, yields a macroscopically homogeneous structure in all its volume, namely a matrix containing a dispersion of the lipophilic granules in a hydrophilic matrix.

[0028] The tablets, capsules and/or minitablets obtained according to the invention can optionally be subjected to known coating processes with a gastro-resistant film, consisting of for example polymers of methacrylic acids (Eudragit®) or cellulose derivatives, such as cellulose acetobutylate.

[0029] The compositions of the invention can contain a high percentage of active ingredient compared with the total composition weight up to 95%, an advantageous characteristic in the case of mesalazine which requires rather high unitary doses.

[0030] In terms of dissolution characteristics, the compositions of the invention provide a release profile of the active ingredient more homogeneous than the traditional systems. In fact, the immediate penetration of water inside the superficial layer of the hydrophilic matrix and the consequent swelling due to the distension of the polymeric chains of the hydrogels, gives rise to a high viscosity hydrated front which prevents the further penetration of water, linearly slowing down the dissolution process to a well determined point which can be located at about half the thickness until the further penetration of water would cause the disintegration of the hydrophilic layer and therefore the release of the content which, consisting of lipophilic granules, however induces the diffusional mechanism typical of these structures and therefore further slows down the dissolution profile of the active ingredient.

[0031] The following examples illustrate the invention in greater detail.
Example 1

[0032] 770 g of 5-aminosalicylic acid are added in a kneader with 20 g of carnauba wax and 50 g of stearic acid with heating until homogeneous dispersion, then extruded into small granules while cold.

[0033] The inert matrix granules are loaded into a mixer in which 30 g of Carbopol 971P and 65 g of hydroxypropyl methylcellulose are sequentially added.

[0034] After a first mixing step for homogeneously dispersing the powders, 60 g of microcrystalline cellulose and 5 g of magnesium stearate are added. After mixing, the final mixture is tabletted to unitary weight of 649 mg/tablet or 510 mg/tablet to obtain 500 and 400 mg dosages, respectively.

[0035] The resulting tablets are film-coated with cellulose acetophthalate or polymethacrylates and a plasticizer to provide gastric resistance and prevent the early release of product in the stomach.

[0036] The dissolution profile of these tablets shows the release of an active ingredient amount lower than 30% within the first hour of permanence in simulated enteric juice, an amount lower than 60% at the fourth hour and an amount lower than 90% at the eighth hour, thus proving that the double matrix effectively controls dissolution.

Example 2

[0037] 1000 g of 5-aminosalicylic acid are added in a kneader with 10 g of carnauba wax and 20 g of stearic acid with heating until homogeneous dispersion, then extruded into small granules while cold or directly granulated in a high rate mixer.

[0038] The resulting granules are loaded into a mixer in which 80 g of hydroxypropyl methylcellulose and 12 g of sodium starch glycolate are sequentially added. After a first mixing step, 11 g of silica colloidal and 11 g of magnesium stearate are added. The final mixture is homogenized, then tabletted to a unitary weight of 1144 mg/tablet.

[0039] The resulting tablets are then film coated with polymethacrylates - or cellulose acetophthalate and plasticizers to provide gastric resistance.

[0040] The dissolution profile of these tablets after a lag time of permanence in the stomach and partly in the intestine provides the release of no more than 35% within the first hour, no more than 50% within two hours, no more than 70% within four hours, no more than 90% within eight hours.

Example 3

[0041] 850 g of 5-aminosalicylic acid are added in granulator/kneader with 9 g of beeswax and 22 g of palmitic acid with heating, until homogeneous dispersion; then worked to a granulate in a high shear granulating device. The resulting granules are then loaded into a mixer with 10 g of carnauba wax and 20 g of stearic acid, until homogeneous dispersion, then cold extruded into small granules while cold.

[0042] The resulting tablets are then film coated with polymethacrylates or acetophthalate of cellulose and plasticizers to provide gastric resistance.

Example 4

[0043] 1100 g of 5-aminosalicylic acid are added in granulator/kneader with 10 g of wax carnauba and 20 g of stearic acid.

[0044] 10 g of polyacrylamide, 39.5 of microcrystalline cellulose and 22 g of colloidal silica are separately loaded into the homogenizer/granulator to obtain a homogeneous solid mixture, which is mixed in the mixer where the active ingredient has been granulated and homogenized.

50.5 g of hydroxypropyl methylcellulose and 12 g of sodium alginate are thoroughly mixed, then added with 5 g of calcium carbonate, 34.5 g of microcrystalline cellulose and 11 g of magnesium stearate. The mixture is homogenized, then tabletted to a final unitary weight of 1194 mg/tablet. The resulting tablets are then film-coated with polymethacrylates or cellulose acetophthalate and plasticizers to provide gastric resistance.

Example 5

[0045] 1200 g of 5-aminosalicylic acid are added in mixer with 10 g of carnauba wax and 20 g of stearic acid, with heating until homogeneous dispersion, then cold extruded into small granules or directly granulated in the high rate mixer.

[0046] The resulting granules are loaded into a mixer, then 70 g of hydroxypropyl methylcellulose and 20 g of sodium starch glycolate are sequentially added.

[0047] After a first mixing step, 80 g of sodium carbonate and 5 g of magnesium stearate are added. The final mixture is homogenized, then tabletted to unitary weight of 1375 mg/tablet.

[0048] The resulting tablets are then film-coated with polymethacrylates or cellulose acetophthalate and plasticizers to provide gastric resistance.
The dissolution profile of these tablets after a lag time of permanence in the stomach and partly in the intestine provides the release of no more than 30% within the first hour, no more than 50% within two hours, no more than 70% within four hours, no more than 90% within eight hours.

Claims

1. A controlled-release oral pharmaceutical composition containing as active ingredient 5-amino-salicylic acid, comprising:

   a) an inner lipophilic matrix consisting of substances with melting point below 90°C in which the active ingredient is at least partly dispersed;
   b) an outer hydrophilic matrix in which the lipophilic matrix and the active ingredient is dispersed;

wherein the composition releases up to 90% of the active agent within 8 hours of immersion in simulated enteric juice.

2. A controlled-release oral pharmaceutical composition containing as active ingredient 5-amino-salicylic acid, comprising:

   a) an inner lipophilic matrix consisting of substances with melting point below 90°C in which the active ingredient is at least partly dispersed;
   b) an outer hydrophilic matrix in which the lipophilic matrix and the active ingredient is dispersed;

wherein the composition releases no more than 30% within the first hour of immersion in simulated enteric juice.

3. A composition according to claim 1 and/or 2 wherein the melting point of the lipophilic matrix is between 40°C and 90°C.

4. A composition according to claim 1 and/or 2 wherein the weight content of the active ingredient in the lipophilic matrix is between 5 to 95%.

5. A composition according to claim 1 and/or 2 wherein the weight ratio of lipophilic matrix to hydrophilic matrix is between 100:0.5 to 100:20.

6. A composition according to claim 1 and/or 2 wherein the hydrophilic matrix is a hydrogel-forming compound.

7. A composition according to claim 1 and/or 2, wherein the lipophilic matrix consists of compounds selected from unsaturated and/or hydrogenated fatty acids, salts, esters or amides thereof, fatty acid mono-, di- or triglycerides, waxes, ceramides, cholesterol derivatives.

8. A composition according to claim 6 wherein the hydrogel-forming compound is selected from polymers or copolymers of acrylic or methacrylic acid, alkylvinyl polymers, hydroxyalkyl celluloses, carboxyalkyl celluloses, polysaccharides, dextrins, pectins, starches and derivatives, alginic acid, natural or synthetic gums.

9. A composition according to any of claims 1 to 8 further comprising a gastro-resistant outer coating.

10. A controlled-release oral pharmaceutical compositions containing as active ingredient 5-amino-salicylic acid, comprising:

   an inner lipophilic matrix consisting of substances with melting point below 90°C selected from unsaturated and/or hydrogenated fatty acids, salts, esters or amides thereof, fatty acid mono-, di- or triglycerides, waxes, ceramides, cholesterol derivatives in which the active ingredient is at least partly dispersed;
   an outer hydrophilic matrix selected from polymers or copolymers of acrylic or methacrylic acid, alkylvinyl polymers, hydroxyalkyl celluloses, carboxyalkyl celluloses, polysaccharides, dextrins, pectins, starches and derivatives, alginic acid, natural or synthetic gums in which the lipophilic matrix and the active ingredient is dispersed and a gastro-resistant outer coating

wherein the weight content of the active ingredient in the lipophilic matrix is between 5 to 95%, the weight ratio of lipophilic matrix to hydrophilic matrix is between 100:0.5 to 100:20, and the composition releases up to 90% of the active agent within 8 hours of immersion in simulated enteric juice.

11. A controlled-release oral pharmaceutical compositions containing as active ingredient 5-amino-salicylic acid, comprising:

   an inner lipophilic matrix consisting of substances with melting point below 90°C selected from unsaturated and/or hydrogenated fatty acids, salts, esters or amides thereof, fatty acid mono-, di- or triglycerides, waxes, ceramides, cholesterol derivatives in which the active ingredient is at least partly dispersed;
   an outer hydrophilic matrix selected from polymers or copolymers of acrylic or methacrylic acid, alkylvinyl polymers, hydroxyalkyl celluloses, carboxyalkyl celluloses, polysaccharides, dextrins, pectins, starches and derivatives, alginic acid, natural or synthetic gums in which the lipophilic matrix and the active ingredient is dispersed and a gastro-resistant outer coating

wherein the lipophilic matrix consists of compounds selected from unsaturated and/or hydrogenated fatty acids, salts, esters or amides thereof, fatty acid mono-, di- or triglycerides, waxes, ceramides, cholesterol derivatives.
carboxyalkyl celluloses, polysaccharides, dex-
trins, pectins, starches and derivatives, alginic
acid, natural or synthetic gums in which the li-
pophilic matrix and the active ingredient is dis-
perssed and
a gastro-resistant outer coating

wherein the weight content of the active ingredient
in the lipophilic matrix is between 5 to 95%, the
weight ratio of lipophilic matrix to hydrophilic matrix
is between 100:0.5 to 100:20, and the composition
releases no more than 30% within the first hour of
immersion in simulated enteric juice.

12. A controlled-release oral pharmaceutical composi-
tion according to claim 1 and/or 2 containing 77% by
weight of 5-aminosalicylic acid, 2% by weight of car-
nauba wax, 5% by weight of stearic acid, 3% by
weight of Carbopol 971 P, 6,5% by weight of hydrox-
propyolphyl methylcellulose, 6% by weight of microcrys-
talline cellulose and 0,5% by weight of magnesium
stearate.

13. A controlled-release oral pharmaceutical composi-
tion according to claim 1 and/or 2 containing 87,41% by
weight of 5-aminosalicylic acid, 0,87% by weight of
carnauba wax, 1,74% by weight of stearic acid,
7% by weight of hydroxypropyolphyl methylcellulose,
1,05% by weight of sodium starch glycolate, 0,96%
by weight of silica colloidal and 0,96% by weight of
magnesium stearate.

Patentansprüche

1. Eine orale pharmazeutische Zusammensetzung mit
kontrollierter Freisetzung, die als aktiven Wirkstoff
5-Amino-Salicylsäure umfasst, umfassend,

a) eine innere lipophile Matrix, bestehend aus
Substanzen mit einem Schmelzpunkt unter 90
°C, in der der aktive Wirkstoff mindestens teil-
weise dispergiert ist;
b) eine äußere hydrophile Matrix, in der die li-
pophile Matrix und der aktive Wirkstoff disper-
giert ist;

wobei die Zusammensetzung nicht mehr als 30 %
innerhalb der ersten Stunde ab der Immersion in si-
muliertem Intestinalsaft freisetzt.

3. Eine Zusammensetzung gemäß Anspruch 1 und/
or 2, wobei der Schmelzpunkt der lipophilen Matrix
zwischen 40 °C und 90 °C liegt.

4. Eine Zusammensetzung gemäß Anspruch 1 und/
or 2, wobei das Gewichtsverhältnis an lipophiler
Matrix zu hydrophiler Matrix zwischen 100:0,5 und
100:20 liegt.

9. Eine Zusammensetzung gemäß einem der Ansprü-
che 1 bis 8, weiterhin umfassend eine enterische
("gastro-resistant") äußere Beschichtung,

10. Eine orale pharmazeutische Zusammensetzung mit
kontrollierter Freisetzung, die als aktiven Wirkstoff
5-Aminosalicylsäure umfasst, umfassend:

a) eine innere lipophile Matrix, bestehend aus Sub-
stanzen mit einem Schmelzpunkt unter 90
°C, in der der aktive Wirkstoff mindestens teil-
weise dispergiert ist;
Eine orale pharmazeutische Zusammensetzung mit

wobei der Gewichtsgehalt des aktiven Wirkstoffs in der lipophilen Matrix zwischen 5 und 95 % liegt, das Gewichtsverhältnis an lipophiler Matrix zu hydrophiler Matrix zwischen 100:0,5 und 100:20 beträgt, und die Zusammensetzung bis zu 90 % des aktiven Wirkstoffs innerhalb von 8 Stunden von der Immersion in simuliertem Intestinalsaft freisetzt.

11. Eine orale pharmazeutische Zusammensetzung mit kontrollierter Freisetzung, die als aktiver Wirkstoff 5-Amino-Salicylsäure umfasst, umfassend:

eine innere lipophile Matrix, bestehend aus Substanzen mit einem Schmelzpunkt unter 90 °C, ausgewählt aus ungesättigten und/oder hydrargyren Fettsäuren, Salzen, Estern oder Amidon davon, Feststücks-Mono-, Di- oder Triglyceriden, Wachsen, Ceramiden, Cholesterolderivaten, in der der aktive Wirkstoff mindestens teilweise dispergiert ist;
eine äußere hydrophile Matrix, ausgewählt aus Polymeren oder Copolymeren der Acrylsäure oder Methacrylsäure, Alkylvinylpolymeren, Hydroxyalkyl-Cellulosen, Carboxyalkyl-Cellulosen, Polysacchariden, Dextrinen, Pectinen, Stärken und Derivaten, Alginsäure, natürlichem oder synthetischem Gummi, wobei die lipophile Matrix und der aktive Wirkstoff dispergiert sind und eine enterische äußere Beschichtung, wobei der Gewichtsgehalt des aktiven Wirkstoffs in der lipophilen Matrix zwischen 5 und 95 % beträgt, das Gewichtsverhältnis an lipophiler Matrix zu hydrophiler Matrix zwischen 100:0,5 und 100; 20 liegt, und die Zusammensetzung nicht mehr als 30 % innerhalb der ersten Stunde ab der Immersion in simuliertem Intestinalsaft freisetzt.


13. Eine orale pharmazeutische Zusammensetzung mit kontrollierter Freisetzung gemäß Anspruch 1 und/oder 2, umfassend 87,41 Gew.% 5-Aminosalicylsäure, 0,87 Gew.% Carnaubawachs, 1,74 Gew.% Stearinsäure, 7 Gew.% Hydroxypropyl-Methyldextrin, 1,05 Gew.% Natrium-Stärkegelatine, 0,96 Gew.% kolloidales Silica und 0,96 Gew.% Magnesium-Stearat.

10. Composition pharmaceutique orale à libération contrôlée contenant, en tant qu’ingrédient actif, de l’acide 5-aminosalicylique, comprenant :

a) une matrice lipophile intérieure constituée de substances ayant un point de fusion inférieur à 90 °C dans laquelle l’ingrédient actif est au moins partiellement dispersé ;
b) une matrice hydrophile extérieure dans laquelle la matrice lipophile et l’ingrédient actif sont dispersés ;
dans laquelle la composition libère jusqu’à 90 % de l’agent actif en l’espace de 8 heures d’immersion dans un suc entérique artificiel.

2. Composition pharmaceutique orale à libération contrôlée contenant, en tant qu’ingrédient actif, de l’acide 5-aminosalicylique, comprenant :

a) une matrice lipophile intérieure constituée de substances ayant un point de fusion inférieur à 90 °C dans laquelle l’ingrédient actif est au moins partiellement dispersé ;
b) une matrice hydrophile extérieure dans laquelle la matrice lipophile et l’ingrédient actif sont dispersés ;
dans laquelle la composition ne libère pas plus de 30 % de l’agent actif au cours de la première heure d’immersion dans un suc entérique artificiel.

3. Composition selon la revendication 1 et/ou 2, dans laquelle le point de fusion de la matrice lipophile est compris entre 40° C et 90° C.

4. Composition selon la revendication 1 et/ou 2, dans laquelle la teneur en poids de l’ingrédient actif dans la matrice lipophile est compris entre 5 et 95 %.

5. Composition selon la revendication 1 et/ou 2, dans laquelle le rapport en poids de la matrice lipophile à la matrice hydrophile est compris entre 100:0,5 et 100:20.

6. Composition selon la revendication 1 et/ou 2, dans laquelle la matrice hydrophile est un composé for-

Revendications

1. Composition pharmaceutique orale à libération contrôlée contenant, en tant qu’ingrédient actif, de l’acide 5-aminosalicylique, comprenant :

a) une matrice lipophile intérieure constituée de substances ayant un point de fusion inférieur à 90 °C dans laquelle l’ingrédient actif est au moins partiellement dispersé ;
b) une matrice hydrophile extérieure dans laquelle la matrice lipophile et l’ingrédient actif sont dispersés ;
dans laquelle la composition libère jusqu’à 90 % de l’agent actif en l’espace de 8 heures d’immersion dans un suc entérique artificiel.

2. Composition pharmaceutique orale à libération contrôlée contenant, en tant qu’ingrédient actif, de l’acide 5-aminosalicylique, comprenant :

a) une matrice lipophile intérieure constituée de substances ayant un point de fusion inférieur à 90 °C dans laquelle l’ingrédient actif est au moins partiellement dispersé ;
b) une matrice hydrophile extérieure dans laquelle la matrice lipophile et l’ingrédient actif sont dispersés ;
dans laquelle la composition ne libère pas plus de 30 % de l’agent actif au cours de la première heure d’immersion dans un suc entérique artificiel.

3. Composition selon la revendication 1 et/ou 2, dans laquelle le point de fusion de la matrice lipophile est compris entre 40° C et 90° C.

4. Composition selon la revendication 1 et/ou 2, dans laquelle la teneur en poids de l’ingrédient actif dans la matrice lipophile est compris entre 5 et 95 %.

5. Composition selon la revendication 1 et/ou 2, dans laquelle le rapport en poids de la matrice lipophile à la matrice hydrophile est compris entre 100:0,5 et 100:20.

6. Composition selon la revendication 1 et/ou 2, dans laquelle la matrice hydrophile est un composé for-
7. Composition selon la revendication 1 et/ou 2, dans laquelle la matrice lipophile est constituée de composés choisis parmi les acides gras insaturés et/ou hydrogénés, les sels, les esters ou les amides de ceux-ci, les mono-, les di- ou les tri-glycérides d’acides gras, les cires, les céramides, les dérivés de cholestérol.

8. Composition selon la revendication 6, dans laquelle le composé formant un hydrogel est choisi parmi les polymères ou les copolymères d’acide acrylique ou méthacrylique, les polymères alkényliques, les hydroxyalkyle celluloses, les carboxyalkyle celluloses, les polyacrylates, les dextrines, les pectines, les amidons et les dérivés d’amidon, l’acide alginique, les gommes naturelles ou synthétiques.

9. Composition selon l’une quelconque des revendications 1 à 8, comprenant, en outre, un revêtement extérieur gastro-résistant.

10. Compositions pharmaceutiques orales à libération contrôlée contenant, en tant qu’ingrédient actif, de l’acide 5-aminosalicylique, comprenant :

- une matrice lipophile intérieure constituée de substances ayant un point de fusion inférieur à 90° C choisies parmi les acides gras insaturés et/ou hydrogénés, les sels, les esters ou les amides de ceux-ci, les mono-, les di- ou les tri-glycérides d’acides gras, les cires, les céramides, les dérivés de cholestérol dans laquelle l’ingrédient actif est au moins partiellement dispersé ; une matrice hydrophile extérieure choisie parmi les polymères ou les copolymères d’acide acrylique ou méthacrylique, les polymeres alkényliques, les hydroxyalkyle celluloses, les carboxyalkyle celluloses, les polyacrylates, les dextrines, les pectines, les amidons et les dérivés d’amidon, l’acide alginique, les gommes naturelles ou synthétiques dans laquelle la matrice lipophile et l’ingrédient actif sont dispersés et un revêtement extérieur gastro-résistant.

- dans lesquelles la teneur en poids de l’ingrédient actif dans la matrice lipophile est compris entre 5 et 95 %, le rapport en poids de la matrice lipophile à la matrice hydrophile est compris entre 100:0,5 et 100: 20, et la composition ne libère pas plus de 30 % au cours de la première heure d’immersion dans un suc entérique artificiel.

12. Composition pharmaceutique orale à libération contrôlée selon la revendication 1 et/ou 2, contenant 77 % en poids d’acide 5-aminosalicylique, 2 % en poids de cire de carnauba, 5 % en poids d’acide stéarique, 3 % en poids de Carbopol 971P, 6,5 % en poids d’hydroxypropyle méthylcellulose, 6 % en poids de cellulose microcrystalline et 0,5 % en poids de stéarate de magnésium.

13. Composition pharmaceutique orale à libération contrôlée selon la revendication 1 et/ou 2, contenant 87,41 % en poids d’acide 5-aminosalicylique, 0,87 % en poids de cire de carnauba, 1,74 % en poids d’acide stéarique, 7 % en poids d’hydroxypropyle méthylcellulose, 1,05 % en poids de sodium, du glycolate d’amidon, 0,96 % en poids de silice colloïdale et 0,96 % en poids de stéarate de magnésium.

11. Compositions pharmaceutiques orales à libération contrôlée contenant, en tant qu’ingrédient actif, de l’acide 5-aminosalicylique, comprenant :